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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,366	12/13/2001	Richard John Bazin	PC10934AGPR	3340

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EXAMINER	
KERR, KATHLEEN M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,366	BAZIN ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/24/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: *copy of ref to Applicant*.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on June 23, 2004), Applicants filed a response and amendment received on September 27, 2004. Said amendment cancelled Claims 21-24. Thus, Claims 1-20 and 25 are pending in the instant Office action.

Election

2. Applicant's election without traverse of Group I, Claims 1-20 and 25, in the reply filed on September 27, 2004 is acknowledged. Claims 1-20 and 25 are pending in the instant Office action and will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the foreign application 0030424.6 filed in the United Kingdom on December 13, 2000 as requested in the declaration. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file.

The instant application is also granted the benefit of priority for the U.S. Provisional Application No. 60/260,627 filed on January 10, 2001 as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statement filed on June 24, 2002 fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following references were not considered for the reasons described below:

a) Anderson *et al.* - No copy provided.
b) Nakamura *et al.* - Wrong citation. JACS articles have the authors at the end. The article from pages 4328-4330 is authored by Hehre *et al.* (see attachment). A correct citation is required for consideration of the reference.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

Compliance with the Sequence Rules

5. A sequence listing was filed on June 6, 2002 and has been entered. However, application fails to fully comply with the requirements of 37 C.F.R. § 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants must provide a statement that the content of the paper and CRF copies filed on June 6, 2002 include no new matter as required by 37 C.F.R. § 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Objections to the Specification

6. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Protein Crystals of AMP Deaminase from Rabbit Skeletal Muscle---

7. The specification is objected to for being confusing incorporating blank pages. Pages 15-16 are blank as filed on December 13, 2001. Applicant is requested to confirm that no information is missing and that these pages are intentionally left blank.

8. The specification is objected to for the brief description of the drawings. The section must be title ---Brief Description of the Drawings--- on page 10, and Figure 3 must be described as Figures 3A-3B for clarity.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 12-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Recitation of specific residues in Claims 12 and 13 are unclear in the absence of a specific SEQ ID NO or a specific data table of crystal structure coordinates. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to any crystal of AMP deaminase having a tetragonal geometry (Claim 1) with optional additional limitations presented in individual, dependent claim form such as: from a particular source or having a particular sequence (or genus of sequences) (Claims 3-5 and 20), space group symmetry $P4_22_12$ (Claim 9), certain cell dimensions (Claim 10), certain structural features (Claims 11-13), or certain resolution (Claim 14). While the structure and function of some species of said genera of AMP deaminase crystals are disclosed in the specification, the common structural characteristics of species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could

predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The specification fully describes three species of AMP deaminase crystals that fall within the instant genera of crystals. Example 3 describes the crystallization of a truncated rabbit AMP deaminase (residues 96-747 of SEQ ID NO:2, see Table 2) in native form; Example 5 describes the use of the Example 3 crystals to soak in coformycin or UK-384,858. All three crystal forms are within the genera of Claims 3-5 and 9-14 based on their sequence, $P4_22_12$ space group symmetry, unit cell dimensions (including error), and resolution (see Tables 1-4).

While the claim language requires a function for the instant genera of crystals (that of AMP deaminase), the claims do not require, and the specification does not describe, any common characteristics that define the structure of the instant genera as a whole. In general, for a species of crystal to be adequately structurally described, the following must be adequately disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein (preferably a SEQ ID NO of all included residues) and any molecule bound to it), (2) the space group, and (3) the unit cell dimensions of the crystal. The three species noted above have adequately met this burden. However, the composition of the crystals encompassed by the breadth of the claims is not described, nor are the space group and unit cell dimensions associated with this breadth of chemical composition described. A singular chemical composition can crystallize differently based on the

crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Based on the instant the specification, the chemical composition, space group, and unit cell dimensions encompassed by the breadth of the claims is unpredictable to one of skill in the art. One of skill in the art would be unable to predict the structure of other members of the genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genera of AMP deaminase crystals are also not adequately described.

11. Claim 25 is rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 25 is drawn to polypeptides having at least 90% identity with SEQ ID NO: 2 (see definition on page 8) with no particular functionality.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could

predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses SEQ ID NO:2 as a rabbit skeletal muscle AMP deaminase. The specification has fully described the genus relating to said SEQ ID NO with both sequence identity limitations and functional limitations (i.e., having AMP deaminase function). However, the genus of the instant claims also contains polypeptides within the sequence identity limitations, but having different function. The specification has not fully described a genus that has sequence identity limitations in the absence of functional limitations. The Examiner suggests the insertion of a functional limitation on the polypeptides in the genus of claim 25.

12. Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for three species of AMP deaminase crystals, does not reasonably provide enablement for any AMP deaminase crystal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The instant claims are drawn to tetragonal crystals of AMP deaminase comprising certain unit cell dimensions (Claim 10) or space group symmetry (Claim 9). To make the crystals and molecules that form crystals encompassed by the scope of the instant claims would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in

Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In order to make the protein crystals encompassed by the scope of the claims, the following must be clear: (a) the preparation and chemical composition of the molecules to be crystallized and (b) the crystallization conditions, including methods and reagents used. Crystallization experiments must be done in order to determine if a macromolecule will crystallize, and X-ray diffraction experiments must be done in order to determine if the crystalline macromolecule is encompassed by the scope of the claims. Small changes in any of the aforementioned factors can change the unit cell dimensions and/or space group symmetry of a crystal dramatically (Giege *et al.*, 1994, noted above); therefore, precise instruction about how to make protein crystals is required so that undue experimentation is not required.

The specification adequately describes how to make three species of tetragonal AMP deaminase crystals that fall within the instant genera of crystals - specifically, rabbit AMP deaminase was purified from a particular source, frozen under certain conditions wherein the N-terminus was truncated (see pages 11-12), then crystallized using vapor diffusion with a protein solution of 15 mg/ml in a buffer of 1.0 M citric acid, 0.10 M imidazole, pH 7.8-8.2 at 20°C (pages 13-14). Said crystals were then exposed to 10 mM coformycin or UK-384,858 to achieve the crystal-inhibitor complexes. Such clear and careful accounting of the crystallization procedure is required and enabled one of skill in the art to also produce these three species of AMP deaminase crystals.

While the state of the prior art provides other means for generally crystallizing rabbit skeletal muscle AMP deaminase (see for example Lee YP. 5'Adenylic acid deaminase. I. Isolation of the crystallize enzyme from rabbit skeletal muscle. J. Biol. Chem. (1957) 227(2): 987-992), specifically tetragonal crystals and/or X-ray quality crystals are not described in the prior art. The specification provides no guidance or other examples for the production of the following: (a) other AMP deaminase crystals of tetragonal shape under conditions other than those described on pages 13-14, (b) AMP deaminase crystals other than that of SEQ ID NO:2 from 96-747, (c) AMP deaminase, and (c) AMP deaminase crystals with a different space group and/or unit cell dimension and/or overall structure (active site, binding pocket, etc.) and/or resolving power. While the quantity of experimentation for the production of novel AMP deaminase crystals other than those described in the instant specification can be extremely high (see Pechkova *et al.* Protein nanocrystallography: a new approach to structural proteomics. Trends in Biotechnology (2004) 22(3): 117-122), it is facilitated by commercially available

crystallization solution screening kits and/or robotics and/or other advances in the field. However, this does not compensate for the high level of unpredictability in the art of crystallizing a protein wherein said crystal is suitable for X-ray analysis because "each protein [not type of protein, like all AMP deaminases, but each individual structure, i.e., SEQ ID NO] requires its own specific conditions [protein concentration, buffer, temperature method of crystallization], which are often difficult to determine and require extensive empirical searching.... For this reason, protein crystallography is often called an art rather than a science" (see Pechkova *et al.*, page 121). Thus, the high level of unpredictability, particularly in light of the additional requirements of the crystals (unit cell, space group, etc.), which cannot be determined until after crystallization is completed, in combination with the quantity of experimentation and the state of the prior art render the instant claims not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 1-20 and 25 are rejected under 35 U.S.C. § 101 because the claimed inventions lack patentable utility. The claims are drawn to crystals of AMP deaminase or the soluble polypeptide. To fulfill the utility requirement of 35 U.S.C. § 101, an invention must have a specific, substantial, and credible utility that is disclosed in the specification or that is well established as considered by one of ordinary skill in the art. While the specification teaches the usefulness of studying the structure of AMP deaminase using the crystalline form of the protein

(see pages 1-2), the specification does not teach one specific, substantial and credible utility for an AMP deaminase crystal itself (or the soluble form of the protein), nor is there a utility well-established in the art. For reference on the utility of protein crystals, see Cases 3 and 4 of the Trilateral Project on protein 3D structure related claims at http://www.uspto.gov/web/tws/wm4/wm4_index.htm.

14. Claims 1-20 are rejected under 35 U.S.C. § 101 because the claimed inventions are directed to non-statutory subject matter. The claims, as written, do not sufficiently distinguish over crystals of AMP deaminase as they naturally exist because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. The claims are drawn to tetragonal crystals of AMP deaminase. Although tetragonal crystals of AMP deaminase can be created in the laboratory, tetragonal protein crystals also occur naturally, *in vivo*; conditions that result in protein crystallization, such as a high local protein concentration and a basic or acidic pH, can occur *in vivo* and can produce the claimed tetragonal crystals. It is not clear that the crystals referred to in the claims are only those engineered in the laboratory. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of "isolated" or "purified" if taught by the specification. See M.P.E.P. § 2105.

15. Claim 25 is rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. Claim 25, as written, does not sufficiently distinguish over polypeptides as they naturally exist because the claims do not particularly point out any non-

naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of "isolated" or "purified" if taught by the specification. See M.P.E.P. § 2105.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claim 25 is rejected under 35 U.S.C. § 102(b) as being anticipated by Smiley *et al.* (see IDS). The instant claim is drawn to a polypeptide having the sequence of SEQ ID NO:2. Smiley *et al.* teach the purification of AMP deaminase from frozen rabbit muscle obtained from Pel-Freez Biologicals, the same source as where Applicant obtained their protein material (see page 11). Thus, the isolated polypeptide of the instant claim inherently has the same structure (SEQ ID NO:2) as that of the prior art.

17. Claim 25 is rejected under 35 U.S.C. § 102(b) as being anticipated by GenBank Accession Number I39444 (AMP deaminase (EC 3.5.4.6) - human. February 21, 1997). The instant claim is drawn to an isolated polypeptide having at least 90% identity with SEQ ID NO:2;

this percent identity is a limitation from the terms "variants, fragments, homologues, analogues, and derivatives thereof" as found in the specification on page 8.

GenBank Accession Number I39444 teaches a protein having a sequence that is 94% identical to SEQ ID NO:2 (see attached alignment).

Conclusion

18. Claims 1-20 and 25 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Primary Examiner
Art Unit 1652

February 22, 2005